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3

Cancer risk in menopausal women

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The incidence for breast and other female-hormone-related neoplasms levels off after menopause. The relative risk (RR) of breast cancer is moderately elevated in current and recent users of hormone replacement therapy (HRT) and increases by about 2.3% per year with longer duration of use, but the effect drops after cessation. Unopposed oestrogen use is strongly related to endometrial cancer risk but cyclic combined oestrogen–progestin treatment appears to reduce this side-effect. However, combined HRT may be associated with higher risk of breast cancer as compared to unopposed oestrogens. Ovarian cancer may also be unfavourably influenced by the use of HRT. HRT has been related to decreased risk of colorectal cancer, the overall RR being about 0.8. Tamoxifen and other selective oestrogen receptor modulators (SERMs) may have a favourable effect on the risk of breast cancer but their risk–benefit profile requires further quantification. The potential effect of 'natural' SERMs (phytoestrogens) on cancer risk remains undefined.

Key words: breast cancer; endometrial cancer; ovarian cancer; colorectal cancer; hormones.

Menopause has a profound effect on the risk of breast and other female-hormone-related cancers, because the slope of incidence for most of these neoplasms levels off after menopause.[1] The incidence of most other epithelial neoplasms, in contrast, continues to increase steadily after menopause.

Age at menopause is a recognized risk factor for breast cancer, with this risk increasing with later age at menopause.[2–4] It is unclear whether latency effects are involved.[5] The most reliable estimate of the influence of age at menopause on breast

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cancer risk was provided by the collaborative re-analysis of individual data from 51 epidemiological studies[6] which estimated an increased risk of 2.8% per year of delayed menopause.

Trends similar to those observed for all menopausal types together were detected in women experiencing a surgical menopause in some studies, although the association was weaker in others.[2,5,7] This is probably attributable to varying definitions of surgical menopause, with some studies including only women with a hysterectomy alone and others also including those with unilateral or bilateral ovariectomy.

Pooled data from two case–control studies conducted between 1983 and 1994 in Italy [8] on 3576 post-menopausal women with incident, histologically confirmed breast cancer, and 3578 post-menopausal controls provided information on the role of age and type of menopause. When all types of menopause were considered together, the floating absolute risks (FARs – which avoid the definition of an arbitrary reference category) were 0.49 for <35 years, 0.81 for 35–39 years, 0.82 for 40–44 years, 0.88 for 45–47 years, 1.02 for 48–50 years, 1.23 for 51–53 years and 1.24 for 54–56 years, with a significant linear trend in risk. A stronger association was observed in women reporting a natural menopause, with FARs of 0.14 for women with menopause <35 years versus 1.20 for those with menopause at 54–56 years (ratio between the two extreme FAR estimates $= 8.6$).

Later menopause has also been associated with increased risks of ovarian[9] and endometrial[10] cancers and perhaps with a reduced risk of colorectal cancer.[11]

Of major concern is the effect on cancer risk of hormone replacement therapy (HRT).[12,13] Total mortality among women who use post-menopausal hormones is lower than among non-users, which probably to a large extent reflects the favourable health characteristics of women who use HRT.[14,15]

HRT, however, also has a number of adverse effects, the main ones being a promotional effect on endometrial cancer and some elevation in the risks of breast and ovarian cancer.[13,15–17]

BREAST CANCER

A summary tabulation of the main risk factors for breast cancer is given in Table 1.

Most information on HRT and breast cancer comes from a re-analysis of individual data from 51 epidemiological studies conducted in 21 countries and including 52 705 women with breast cancer and 108 411 controls.[6] This showed a 2.3% (95% confidence interval, CI, 1.1 to 3.6%) increase in the relative risk (RR) of breast cancer for each year of HRT use. This corresponds to a RR of 1.35 (95% CI 1.20 to 1.49) for current users who had used HRT for 5 years or more, and to a cumulative excess for women who began use of HRT at age 50 of approximately two cases/1000 women for 5-year users, six cases/1000 women for 10-year users, and 12 cases/1000 women for 15-year users. This increase was comparable with the effect on breast cancer of later menopause. This elevated risk, however, levelled off after stopping HRT use, with no material excess risk five or more years after stopping, as compared to never users.

Use of HRT for a short time (i.e. <5 years) to control menopausal symptoms is not related to any material increase in the risk of breast cancer.[6] The biological mechanism underlying this association remains unclear.[18] Changes in the composition of the breast tissue have been documented, with a greater mammographic density having been noted following hormone use.[19]

Table 1. Summary of major risk factors for breast cancer.

Factors influencing risk	Estimated relative risk[a]
Residency in urban areas	1.5
White race	2
Higher levels of education or income	1.5
Mother or sister with breast cancer	2–3
Nulliparity or late ages at first birth ($\geqslant$30 versus $<$20 years)	2–3
Absence of breastfeeding for long durations	1.5
Early ages at menarche ($<$13 versus $\geqslant$15 years)	1.5
Late ages at natural menopause ($\geqslant$55 versus $<$45)	2
Recent use of oestrogens or combined oestrogen–progestin therapy	2
Use of oral contraceptives (pre-menopausal risk only)	1.5–2
High cumulative doses of tamoxifen	0.5
Biopsy-confirmed proliferative breast disease or dense mammographic patterns	2–5
Obesity (post-menopausal risk only) (body mass index $\geqslant$28 versus $<$22)	2
Radiation to chest in moderate to high doses	1.5–2
History of breast cancer in one breast	2–4
History of primary cancer in endometrium, ovary	1.5–2

[a]Relative risks depend on the population under investigation and referent group employed.

Another open question is the impact on the risk of breast cancer of the combination of oestrogens and progestins, a therapy effective in reducing the excess endometrial cancer risk associated with oestrogen use alone.[20] There are biological reasons to suspect an unfavourable effect of added progestins on breast carcinogenesis, because ovulatory cycles are related to the risk of breast cancer and breast mitotic activity is higher during the luteal phase of the cycle.[21] An early report of a Swedish cohort study[22] suggested that combined HRT may be more strongly related to the risk of breast cancer than oestrogens alone, with a non-significantly elevated RR of 1.2 for ever use and of 4.4 for more than 6 years use, based on 10 cases only (95% CI, 0.9 to 22.4). An update of the same study[23] confirmed these findings, showing RRs of 1.4 after 1–6 years and 1.7 after more than 6 years of use of combined preparations. The excess risk, however, appeared confined to recent users. Three other studies from Britain[24], Denmark[25] and Sweden[26] showed an association between combined HRT and breast cancer. A report from the American Nurses Health Study cohort[27] confirmed some excess risk of breast cancer among current long-term HRT users: the RRs were 1.3 (95% CI 1.1 to 1.5) for conjugated oestrogen users, 1.3 (95% CI 1.0 to 1.7) for other oestrogen users and 1.4 (95% CI 1.2 to 1.7) for oestrogen plus progestin. A case–control study in Sweden, involving 3345 women with breast cancer, found an increasing risk with duration of different types of combined oestrogen–progestin use (RR = 2.4 for women treated for at least 10 years).[28]

A report on 46 355 participants followed for a mean of 10.2 years in the Breast Cancer Detection and Demonstration Project showed that women who had used combined oestrogen and progesterone had a 40% increased incidence rate (95% CI = 1.1–1.8) of developing breast cancer compared with never-users.[29] The risk from combined therapy was greater than that observed with unopposed oestrogen (20% increase in risk, 95% CI 1.0–1.4). The increased risk was limited to use within the previous 4 years. The increased risk was also largely confined to women with a body mass index of 24.4 or less, which indicates that there could be a threshold effect of

HRT because heavier women are likely to have a higher average level of endogenous oestrogen that in itself increases risk.

Similarly, a population-based case–control study of 1897 post-menopausal cases and 1637 population controls from Los Angeles County[30] found a RR of 1.06 (95% CI 0.97 to 1.15) for each 5 years of oestrogen replacement therapy use – but of 1.24 (95% CI 1.07 to 1.45) for combined oestrogen–progestin treatment.

A case–control study from Washington state[31] suggested that combined HRT increases the risk of lobular, but not ductal, breast carcinoma, but the findings were inconclusive.

Another major issue is the time-risk relation after stopping HRT. The effect of steroid hormones is thought to be on the later stages of carcinogenesis (i.e. they are promoters)[32]; consequently, the increased risk of breast cancer associated with HRT declines within a few years after stopping use.

Although the absence of a long-term cumulative risk is reassuring, a 20–30% excess risk of breast cancer in women aged 50 to 65 years – when HRT use is most frequent – has to be weighed against the benefits of HRT on the bone and perhaps on the cardiovascular system.[33]

Another open question is whether the relationship between HRT and the risk of breast cancer differs at various ages. Because there are indications that it is influenced by age at diagnosis, with a higher relative risk in older women[27,34], any risk–benefit ratio is particularly critical and must be carefully and individually assessed for elderly women.[35,36] In the re-analysis of individual data from the 51 studies, no significant interaction was observed between the RR for HRT use and age[6], although elderly women were at a greater absolute risk of breast cancer given increasing incidence with age.

There are no data from clinical trials on the HRT–breast cancer association, but the Postmenopause Oestrogen/Progestin Intervention (PEPI) trial reported that increased mammographic density was observed in 3.5% of the oestrogen-only group, but in 16–23% of the different oestrogen/progestin schedules.[37]

Although hormone replacement therapy has been associated with an increased incidence of breast cancer, use appears to lead to lower mortality from breast cancer or improved prognosis in some[38–40], although not all[14,41], studies. Although some of this effect may be due to increased breast cancer surveillance among hormone users, a favourable biological effect of hormone use on the biological characteristics of breast neoplasms cannot be dismissed.[40,42]

In the American Cancer Society Cancer Prevention Study II, breast cancer mortality did not increase with oestrogen use overall, and no excess mortality was observed for thin or heavy women.[43]

Although a diagnosis of breast cancer has been conventionally viewed as a contraindication for subsequent HRT use, this notion is being questioned given data showing favourable effects of HRT on breast cancer prognosis.[44] Although the few studies that have addressed this issue seem to indicate no adverse effects of HRT usage among breast cancer survivors, sample sizes have been limited.[45]

ENDOMETRIAL CANCER

A summary tabulating the main risk factors for endometrial cancer is given in Table 2.

An association of endometrial cancer with menopausal HRT was suggested on the basis of a substantial rise in the incidence of endometrial cancer seen in the United States (particularly in California) in the early 1970s, following widespread use of HRT.[10]

Table 2. Summary of major risk factors for endometrial cancer.

Factors influencing risk	Estimated relative risk[a]
Residency in North America or Europe versus Asia	4–5
White race	1.5–2
Higher levels of education or income	1.5–2
Nulliparity	3
History of infertility	2–3
Menstrual irregularities	1.5
Early ages at menarche (<13 versus ⩾15 years)	1.5–2
Late ages at natural menopause (⩾55 versus <45 years)	2
Long-term use or high dosages of menopausal oestrogens	10–20
Use of oral contraceptives	0.3–0.5
High cumulative doses of tamoxifen	3–7
Obesity (body mass index ⩾28 versus <22)	2–5
Stein–Leventhal disease or oestrogen–producing tumours	>5
Histories of diabetes, hypertension, gallbladder disease or thyroid disease	1.3–3

[a]Relative risks depend on the population under investigation and referent group employed.

The risk is about two to three times greater in ever-users than in never-users of oestrogens, with a summary RR from a meta-analysis of published studies of 2.3 (95% CI 2.1 to 2.5) [46]; the risk estimates were similar for cohort (RR 1.7) and case–control studies using hospital (RR 2.2) or population (RR 2.4) controls. The risk was related to duration of use: the RR was 1.4 for use <1 year, 2.8 for 1 to 5 years, 5.9 for 5–9 years and 9.5 (95% CI 7.4 to 12.3) for ⩾10 years.[46] The risk was also inversely related to time since last use[46], suggesting that oestrogens have a late-stage effect in endometrial carcinogenesis.[32,47]

Oestrogen-associated risks for endometrial cancer tend to be higher in leaner than overweight women, suggesting that exogenous oestrogens and obesity act through similar biological mechanisms on the risk of the disease.[48] Some studies suggest a greater excess risk of HRT among smokers[49,50], who tend to have lower oestrogen availability, and a lower HRT-related risk among women who had a history of use of combined oral contraceptives.[50,51] Shields et al[52], however, failed to delineate a subgroup that is exempt from the increased risk of endometrial cancer associated with use of unopposed oestrogens.

Data on type, dose or regimen of oestrogen use are inconsistent, and in general there appears to be no clear association with type of preparation, its potency and bioavailability, dose and duration, although users of high-dose preparations tend to have a higher risk.[50] In the meta-analysis by Grady et al[46] the RR was 3.9 (95% CI 1.6 to 9.6) for users of 0.3 mg conjugated oestrogens, 3.4 (95% CI 2.0 to 5.6) for users of 0.625 mg and 5.8 (95% CI 4.5 to 7.3) for users of ⩾1.25 mg. As for the type of compound used, the RR was 2.5 for users of conjugated oestrogens and 1.3 for users of synthetic oestrogens. With reference to pattern or regimen of use, the RR was 3.0 for intermittent and cyclic use and 2.9 for continuous regimens.[46]

Unopposed oestrogen treatment was associated with over 50% of cases of endometrial cancer in North America in the late 1970s[53] and 10 to 25% of cases in Europe in the 1980s.[51,54]

The cyclic addition of progestins to oestrogens protects against endometrial hyperplasia, which is considered an endometrial cancer precursor.[20]

The summary RR from a meta-analysis[46] of endometrial cancer in women using cyclic combined therapy was 0.8 (95% CI 0.6 to 2.2). However, the results from cohort and case–control studies were inconsistent, with the pooled RR being 0.4 for cohort studies and 1.8 for case–control studies.

The number of days per month of progestin addition is an important determinant of risk. One study[55] suggested that the RR was reduced from 2.4 to 1.1 for women using progestins for 10 days or more per month. In a population-based case–control study including 832 cases and 1114 controls[56] the RR for ever-users was 3.1 for women with fewer than 10 days of added progestins per month and 1.3 (95% CI 0.8 to 2.2) for those with 10–21 days of added progestins. Another study on 833 cases and 791 population controls from Los Angeles County[57] showed RRs per 5 years of use of 2.2 for unopposed oestrogens, 1.9 for oestrogens plus progestins for less than 10 days per month, and 1.1 (95% CI 0.8 to 1.4) when progestins were given for 10 days or more.

A study conducted in Sweden on 709 cases of endometrial cancer in post-menopausal women and 3368 controls[58] confirmed a strong association with unopposed oestrogens (RR = 6.2 for oestradiol and 6.6 for conjugated oestrogens for 5 or more years of use). The association was considerably less strong for the combination of oestrogens and progestins (RR = 1.6, 95% CI 1.1–2.4), and the risk was below unity for continuous use of progestins (RR = 0.2, 95% CI 0.1–0.8 for use lasting 5 years or longer).

Similarly, a record linkage study conducted in Sweden on a cohort of 8438 women at risk of endometrial cancer[23] showed – on the basis of 66 observed cases versus 34.8 expected – a RR of 4.2 (95% CI 2.5–8.4) for 6 years or more of use of unopposed oestrogens, and of 1.4 (95% CI 0.6–3.3) for combined oestrogen and progestin therapy.

In a study of 512 cases of endometrial cancer and 513 controls conducted between 1994 and 1998 in Ontario, Canada, the RR was 4.1 (95% CI 2.2–7.7) for use of >5 years unopposed HRT, and around 1.5 for various types of combined therapies, although numbers of subjects were small in most subgroups.[59]

The use of long-cycle (3-month) HRT was associated with a greater endometrial cancer risk (RR = 2.0), as compared to monthly cycle HRT (RR = 1.3) according to a nationwide cohort study from Finland.[60]

Thus, although the use of oestrogens alone may increase endometrial cancer risk, several studies indicate that combined therapy is not related to a major excess of endometrial cancer if progestins are given for more than 10 or 14 days in each cycle.[61]

OVARIAN CANCER

Descriptive studies are consistent with the absence of a major effect of HRT on ovarian carcinogenesis.[13,62]

Two cohort studies showed no association between the use of HRT and the risk of ovarian cancer, including the Walnut Creek Study on Contraception[63], based on 16 638 women followed-up for 13 years (RR = 1.0), and a Swedish cohort study[64], based on 23 246 women followed-up for an average 8.6 years (RR = 0.99, 95% CI 0.76 to 1.27). In contrast, in the American Cancer Society Cancer Prevention Study II[65], based on mortality data of 243 073 women followed-up for $\geqslant 11$ years, the RR was 1.71 (95% CI 1.06 to 2.77). The 14-year follow-up of the CPS-II study[66] confirmed the association between HRT and ovarian cancer. The RR was 1.5 (95% 1.2–2.0) for ever use and 2.2 (05% CI 1.5–3.2) for baseline users for $\geqslant 10$ years. Among former users, the RR decreased with time since last use.

Several case–control studies have provided data on HRT and ovarian cancer risk. Of these, one study from the USA[67], a multicentre case–control study from various areas in the USA[68], a population-based case–control investigation from Canada[69], and four European studies from the UK, Greece and Italy, reported RRs above unity, i.e. between 1.2 and 1.6.[70] Other case–control studies found no clear relation between ever-use of HRT and ovarian cancer risk.[71] The combined analysis of individual data from 12 case–control studies in the USA, based on 2197 white women with invasive epithelial ovarian cancer and 8893 white controls[72], found a multivariate RR for ever HRT use of 0.9 in hospital-based and 1.1 in population-based studies. The RR for ever HRT use was 1.1 in a re-analysis of original data considering 327 cases of borderline epithelial ovarian cancers.[73] A collaborative re-analysis of four European studies from the UK, Italy and Greece, based on 1470 ovarian cancer cases and 3271 hospital controls, found a RR of 1.71 (95% CI 1.30–2.25) for ever HRT use, a positive association with duration of use, and some indication that the excess relative risk for ovarian cancer declined with time since last use.[70] The overall RR estimate from a meta-analysis of published data was 1.15 (95% CI 1.0–1.3) for ever use and 1.27 (95% CI 1.0–1.6) for >10 years use.[74]

Very little information is available on the addition of progestins to oestrogen preparations. In a cohort of 4544 women, recruited since 1978 from 21 menopause clinics in Britain and followed-up to 1988[38], no association emerged with ovarian cancer risk (RR $= 0.63$); similarly, in a multicentre case–control study of 377 cases and 2030 controls conducted between 1976 and 1985 in various areas in the USA[68], only 2% of cases and controls had ever used combination HRT, and the multivariate RR was 0.7 (95% CI 0.2 to 1.8).

Thus, a moderate positive association remains possible between HRT and epithelial ovarian cancer.

COLORECTAL CANCER

Colorectal cancer is the most frequent cancer site in non-smokers of both sexes combined in western countries.[62,75] Over the last two decades, mortality rates from colorectal cancer in many developed countries have declined in women more than in men.[62] A role of exogenous female hormones on these trends is possible.[71]

Eight cohort studies[39,76–85] (see Table 3) reported information on HRT use and the risk of colorectal cancer including over 2400 cases. Most studies showed RRs around or below unity.[86] A significant inverse association was found in two cohort investigations, including the largest one focusing on fatal colon cancers. HRT use may also improve short-term survival after a diagnosis of colon cancer.[87]

A meta-analysis of 20 studies published up to December 1996[88] found an overall RR for ever HRT use of 0.85 (95% CI: 0.7–0.9). The protection was greater for current or recent users (RR 0.69, 95% CI: 0.5–0.9) and users of more than 5 years (RR 0.73, 95% CI: 0.5–1.0).

A causal interpretation of the above findings is, however, hampered by (1) the time risk pattern observed; (2) the potential for prevention (i.e. a more favourable pattern of risk factor exposure) bias[89] or surveillance bias in women taking HRT[90]; and (3) lack of clear understanding of the possible mechanisms of action of HRT on colorectal mucosa.

Post-menopausal women treated with HRT tend, however, to be of higher social class and are more educated.[36,89,91] This selection may imply a healthier lifestyle (e.g. more frequent consumption of vegetables, higher levels of physical activity, and lower prevalence of overweight). In addition, long-term HRT users are, by definition, compliant, which is, per se, a favourable health indicator.[89]

Table 3. Cohort studies on hormone replacement therapy (HRT) and colorectal cancer.

Reference	Country	Population, (follow up), no. cancer		Relative risk, RR (95% confidence interval) (ever vs. never users)		
				Colon–rectum	Colon	Rectum
Wu et al 1987[76]	California, US	7345 (4 years) 68		1.00 (n.s.)		
Adami et al 1989[77] and	Sweden	22 597 (13 years)	HRT	–	0.9 (0.7–1.1)	0.9 (0.7–1.2)
Persson et al 1996[39]		233	Oestriol		1.0 (0.8–1.3)	0.8 (0.5–1.2)
		62 deaths				
			Opposed HRT		0.6 (0.4–1.0)	0.8 (0.4–1.3)
			Any type	–	0.9 (0.7–1.2)	0.9 (0.7–1.1)
Chute et al 1991[78] and	US, Nurses'	59,002 (14 years)	Current users	0.7 (0.5–0.8)	0.6 (0.5–0.9)	0.7 (0.4–1.1)
Grodstein et al 1998[79]	Health Study	470	Past users	0.8 (0.7–1.1)	0.9 (0.7–1.1)	0.8 (0.5–1.2)
Bostick et al 1994[80] and	Iowa, US	41,837 (6 years)	Former users		0.8 (0.6–1.1)	
Folsom et al 1995[81]		293	Current users		0.7 (0.5–1.1)	
Calle et al 1995[82]	US, Cancer	422 373 (7 years)	–		0.7 (0.6–0.8)	
	Prevention Study II	897 deaths				
Risch and Howe 1995[83]	Canada	32 973 (14 years) 230		1.0 (0.7–1.5)	1.3 (0.9–1.9)	0.6 (0.3–1.2)
Troisi et al 1997[84]	US, BCDDP	33 779 (7.7 years)	Unopp. HRT	–	1.1 (0.7–1.5)	1.2 (0.7–2.3)
		313	Opposed HRT		1.4 (0.7–2.5)	–
			Any HRT	0.99 (0.79–1.2)	1.1 (0.81–1.6)	1.1 (0.59–1.9)
Paganini-Hill, 1999[85]	USA Leisure			0.81 (0.63–1.04)	0.70^{+} (0.45–1.09)	0.52^{+} (0.21–1.31)
	World Cohort	7,701 (14.5 years) 249				

BCDDP = Breast Cancer Detection Demonstration Project.
BMI = Body Mass Index.
W/H = Waist/Hip.
OC = Oral Contraceptives.
$^{+}$Recent users ($\leqslant$ 1 year).

Sex hormones modify hepatic cholesterol production and alter bile acid concentration.[92] Secondary bile acids are believed to favour malignant changes in the colonic epithelium, and exogenous oestrogens, which decrease secondary bile acid production and can alter intestinal microflora, could, therefore, protect against colorectal cancer. Further, methylation-associated inactivation of the oestrogen receptor (ER) gene in ageing colorectal mucosa could predispose to colorectal tumorigenesis.[93]

In western countries, the numbers of deaths from colorectal and breast cancers in women aged 55 or older are similar (27 000 and 34 000, respectively, in 1994 in the United States). Thus, a decrease in incidence or mortality from colorectal cancer could greatly affect the balance of risks and benefits associated with the use of HRT.

OTHER NEOPLASMS

A cohort study in Sweden of 23 244 women followed for 6.7 years suggested a slight excess risk of lung cancer associated with use of oestrogens (RR = 1.3, 95% CI 0.9–1.7).[77] Two case–control studies in the USA have also examined the relation of HRT use to the risk of adenocarcinomas of the lung, providing inconclusive results.[13]

In a Swedish cohort study[77] a total of 13 cases of biliary tract and liver cancers were observed versus 39.7 expected, corresponding to an RR of 0.4 (95% CI 0.2 to 0.7). In an Italian case–control study, based on 82 histologically confirmed cases of primary liver cancer and 368 controls, a non-significant decrease in risk associated with HRT was also noted (OR = 0.2, 95% CI 0.03 to 1.5).[94] However, no association between conjugated oestrogen and other oestrogen use and hepatocellular carcinoma was observed in another case–control study involving 74 cases and 162 population controls from Los Angeles County[95]: the RR was 1.1 for ever-use and 1.0 for >5 years use.

The effects of HRT on other cancers, including stomach, pancreas and skin melanoma, are inconsistent.[13] A suggestion of an inverse relation between HRT use and cervical cancer[96] requires confirmation.

OTHER THERAPEUTIC APPROACHES

Given the recognized adverse effects of HRT, recent attention has focused on assessing alternative approaches to treating the menopause, including the use of tamoxifen and other selective oestrogen receptor modulators (SERMs). These agents are recognized anti-oestrogens, which presumably will offer many of the same advantages as HRT while eliminating some of the disadvantages (no increase in the risk of breast cancer). In fact, the available data seem to indicate that these agents offer substantial advantages in terms of reducing the risk of breast cancer.

In the National Surgical Adjuvant Breast and Colorectal Project (NSABP), 13 388 US women who were 60 years of age or older, or who had a 5-year risk of 1.66% or more of developing breast cancer, or who had a history of lobular carcinoma in situ, were randomly assigned to receive 20 mg daily of tamoxifen or placebo for 5 years.[97] After 69 months of follow-up, women receiving tamoxifen had a 49% lower risk of invasive breast cancer than did placebo-treated women. Some adverse effects of tamoxifen, however, were noted in the trial, including excess risks of endometrial cancer, stroke, pulmonary embolism and deep-vein thrombosis, events that occurred more frequently in women aged 50 years or older.

Two other clinical trials of tamoxifen in breast cancer prevention have presented interim results. In a British trial, 2494 women aged 30 to 70 years with a family history of breast cancer were randomly assigned to tamoxifen or placebo and followed for up to 8 years.[98] The risk of invasive or in situ breast cancer was 1.06 in the group given tamoxifen compared to the group given placebo. A difference between this and the US trial study was that the British women were allowed to use HRT during the trial (about one-third of study participants were users). In a trial conducted in Italy, 5408 women who had a hysterectomy were randomized to 5 years of tamoxifen or placebo.[99] After a median of 46 months follow-up, there was no difference in breast cancer incidence by treatment arm. Despite the inconsistent trial results, the US FDA has approved the use of tamoxifen for reducing the risk of breast cancer in high-risk women.

Less information is available on other SERMs. In the Multiple Outcomes of Raloxifene Evaluation (MORE) trial of 7705 post-menopausal osteoporotic women under the age of 81, 60 or 120 mg of raloxifene daily decreased breast cancer risk by 76% (RR = 0.24, 95% CI 0.1–0.4) as compared to non-users.[100] The risk for thromboembolic disease was increased threefold, but there was no increased risk for endometrial cancer in raloxifene-treated compared with placebo-treated women. The US National Cancer Institute and the NSABP are now conducting a large, multicentre study to test tamoxifen versus raloxifene to determine whether raloxifene shows the same risk reduction as tamoxifen, and to determine whether the risk for adverse events differs.

Research is also beginning to focus on whether more natural approaches to treating the menopause should be recommended. Although there is growing enthusiasm for the use of phytoestrogens, termed by some as 'natural' SERMs, their effects on cancer risk remain unresolved.

SUMMARY

HRT use is associated with a moderately excess risk of breast cancer, but the increased risk appears to be restricted to current users. Combined HRT may be associated with

Practice points

- HRT use is associated with a moderate excess risk of breast cancer. It is unclear whether risk is related to duration of use, but the increased risk appears to be restricted to current users. Combined HRT may be associated with a higher risk of breast cancer as compared to unopposed oestrogens
- the patten of risk appears similar for ovarian cancer, but is less well defined
- oestrogens are strongly associated with the risk of endometrial cancer. Combined therapy, however, is not related to risk if progestins are given for more than 10–14 days per cycle
- HRT may reduce the risk of colorectal cancer, but further research is required to confirm this effect and clarify possible biological mechanisms
- there is no consistent association between HRT and lung, liver or other digestive neoplasms, or melanoma
- the SERM tamoxifen appears to reduce the risks of some types of breast cancer, but increases the risk of endometrial cancer. Less is known regarding the relationship of other SERMS, including the so called 'natural' ones, to cancer risk

Research agenda

- further quantify the risk of breast cancer with the combination of oestrogens and progestins
- better understand whether the relationship between HRT use and the risk of breast cancer differs at various ages
- further investigate a potentially favourable effect of hormone use on the biological characteristics of breast tumours
- understand the potential role of HRT in women with a diagnosis of breast cancer
- better quantify the risk of combined therapy with the risk of endometrial cancer
- provide further data on ovarian, colorectal, lung and liver cancer
- evaluate the use of tamoxifen and other SERMs, and perhaps more natural approaches, in treating the menopause

higher risk of breast cancer as compared to unopposed oestrogens. A similar pattern of risk may be present for ovarian cancer, but the data are still inconclusive. Oestrogens are strongly associated with endometrial cancer risk. Combined therapy, however, is not related to risk, if progestins are given for more than 10–14 days per cycle. HRT may reduce the risk of colorectal cancer, but further research is required to confirm this effect and clarify possible biological mechanisms. There is no consistent association between HRT and lung, liver or other digestive neoplasms or melanoma. The SERM tamoxifen appears to reduce the risks of some types of breast cancer but increases the risk of endometrial cancer. Less is known regarding the other SERMs, including the so-called natural SERMs, and cancer risk.

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